REMARKS

Claims 46-66 are currently pending. Claims 46-55 and 64-66 stand rejected, claims 56-63 are withdrawn and claim 66 has been cancelled. Claims 46, 54-55 and 65 are amended herein. Support for the amended claims can be found throughout the specification and claims as originally filed. No new matter is presented.

The withdrawal of claims 56-63 and cancellation of claim 66 is not a disclaimer of the subject matter of those claims. The Applicant reserves the right to pursue the subject matter of those claims in a different application or in future continuing applications.

Information Disclosure Statement

The Applicant notes the examiner's indication that reference 235 on PTO 1449, filed May 7, 2005 has not been considered because volume number and date of publication are purportedly missing from the 1449 form. A copy of this reference accompanies the present reply, in addition to a copy of the 1449 form submitted May 7, 2005, for the examiner's consideration. Consideration and acknowledgement thereof by the examiner is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

A. Enablement

Claims 46-55 and 64-66 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly not enabled. The Examiner appears concerned that the specification "does not teach how to make any 'antagonist antibody' having the properties of blocking excessive apoptosis . . . or blocking any Apo-3 receptor mediated activation of NF-κB activation . . .." Office action, page 5. The Examiner also appears concerned that the use of the term "comprising" in the present claims encompasses an "unlimited undisclosed antigen binding sites." Office action, page 6. The Examiner cites a purported lack of working examples in support of the conclusions presented in the instant Office action. *See id.*

It is important to note that the Examiner has acknowledged enablement for "a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized [sic] an antibody or antigen binding fragment thereof that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising

the amino acid residues 1 to 417 of SEQ ID NO:47[1] [sic], the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO:6, the death domain of Apo-3 consisting of the amino acid residues 338 to 417 of SEQ ID NO:6 and a method of detecting Apo-3 using said antibody . . ." *Id.* at page 3. Moreover, the Examiner acknowledges enablement for use of these antibodies "to block excessive apoptosis" or "block potential autoimmune/ inflammatory effects of Apo-3 resulting from NF-κB activation." *See id.* at page 4. Applicant submits that if the use of antibodies to the full-length, extracellular domain and death domain of Apo-3 polypeptide and the use of Apo-3 antibodies to block apoptosis and NF-κB activation are enabled by the specification, such *antibodies per se* are enabled by the specification.

Furthermore, the claimed antibodies are both structurally and functionally limited. They are structurally limited, for example, because an antigen binding site that binds to an Apo-3 receptor polypeptide comprising SEQ ID NO:6 or an immunogenic fragment thereof is required. They are functionally limited, for example, because blocking or inhibition of Apo-3 receptor induced apoptosis or Apo-3 receptor activation of NF-κB is required. The specification adequately teaches one of skill in the art how to make and use such antibodies.

For example, the specification identifies and characterizes the Apo-3 receptor both structurally and functionally. *See, e.g.,* SEQ ID NO:6 and Examples 5-10. In addition, methods are described in the specification for preparing polyclonal, monoclonal, humanized, bispecific and heteroconjugate antibodies. *See, e.g.,* specification pages 53-61. Based on the teachings in the specification and the knowledge in the art at the time of filing, the subset of antibodies defined in the claims are contemplated and enabled by the present disclosure.

The fact that SEQ ID NO:6 defines a polypeptide having 417 amino acid residues (*i.e.*, the claims contain open-ended "comprising" language) is not determinative of undue experimentation because making and using the antibodies within the scope of the claims involves both structural and functional limitations. As indicated, for example, on page 54, "the immunizing agent will typically include the Apo-3 or Apo-2LI polypeptide or fusion partner thereof." The specification teaches that an Apo-3 polypeptide immunogen encompasses "the native sequence Apo-3 and Apo-3 variants," including Apo-3 fragments. *See, e.g.,* at pages 13-14. The claims specify that when the antibody binds an Apo-3

[1] They Applicant assumes that since SEQ ID NO:47 does not appear in the present

fragment, it must be an immunogenic Apo-3 fragment and the resulting antibody must block or inhibit, for example, apoptosis. As one of skill in the art would appreciate, an immunizing agent must be immunogenic in a host in order to generate antibodies.

The Examiner's citation of the Stryer et al., Kuby et al. and Abaza et al. references is unavailing to the position set forth in the Office action. The fact that routine experimentation may result in the preparation of some antibodies that may not fulfill the limitations of the claims should not detrimentally affect the determination that the pending claims are enabled for their scope. Experimentation may not be considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation – time and difficulty are not determinative of undue experimentation if the experimentation is routine. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); see also In re *Wands*, 858 F.2d 731, 736-40, 8 USPQ2d 1400, 1403-07 (Fed. Cir. 1988); MPEP § 2164.06.

The Examiner has appeared to read a "treating" limitation into the present claims, *e.g.*, "the specification does not teach how to make any 'antagonist antibody' . . . for treating any neurological disease or . . . for treating autoimmune/inflammatory effects . . .." Office action, page 5. This is inappropriate as the claims require only "blocking or inhibiting" certain activities of the Apo-3 receptor. The fact that certain conditions may be *treated* utilizing the methods of the present invention is irrelevant to the issue of enablement because *treatment* is not a requirement of the claims. As such, the citation of the Coney et al. reference is unavailing.

With regard to claims 52-53 the Examiner questions how a labeled antibody can effect the blocking or inhibition required in the present claims. *See* Office action, page 6. The applicant respectfully submits that this added limitation could be readily and routinely performed by one of skill in the art. It is well known in the art that an antibody can be labeled without affecting its reactivity or binding specificity in, for example, a sandwich assay, a competitive binding assay or an immunoprecipitation assay. *See, e.g.*, specification at page 62. This antibody may be labeled and used to bind a receptor, for example, an Apo-3 polypeptide receptor. Although complement may be affected due to the means utilized to label the antibody, complement is not required to fulfill, for example, the blocking limitation

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application, the Examiner intended to refer to SEQ ID NO:6 instead of SEQ ID NO:47.

of the claims. If the labeling process affects the ability of the antibody to block the selected activity, this too can be determined utilizing methods set forth in the specification and the resulting labeled antibody would be excluded from the claims as not having the requisite activity. Accordingly, given that antibody labeling may be routinely performed, the Applicant respectfully submits that claims 52 and 53 are enabled.

With regard to claim 65, the Examiner questions how an antibody can bind the disclosed death domain since it lies within the intracellular domain of the Apo-3 polypeptide. *See id.* Although the present disclosure discusses secreted active forms of Apo-3 that can be blocked or inhibited utilizing an anti-Apo-3 antibody, the requirement for secretion is not required in the claim. Moreover, an anti-Apo-3 intrabody, a type of antibody well-known in the art at the time of filing, could have been routinely utilized to target intracellular protein regions such as the death domain. In this regard, the Applicant notes that the term "antibody" is used in its broadest sense in the specification. Applicant, nevertheless, has amended claim 65, as shown above, to clarify the presence of the recited death domain in the Apo-3 polypeptides provided in claim 64.

Applicant's cancellation of claim 66 renders the rejection of the claim moot.

For the reasons discussed above, the Applicant respectfully submits that the present claims are enabled and the rejection should be withdrawn.

B. Written Description

Claims 46-55 and 64-66 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly not supported by an adequate written description. The Examiner appears concerned that "there is insufficient written description about any and all Apo-3 antibody that has the property of blocking or inhibiting Apo-3 receptor induced apoptosis and/or Apo-3 receptor activation of NF-κB activation for the claimed method." Office action, page 7. Similar to the enablement rejection discussed above, the Examiner expresses concern over the use of the term "comprising" in claims 64 and 65 as it encompasses amino acid residues of the Apo-3 polypeptide in addition to those regions specifically recited. *See id.*

Again, it is important to note that the Examiner has indicated that "[t]he specification discloses only a method of affinity purification of Apo-3 from recombinant cell culture or natural sources comprising immobilized [sic] an antibody or antigen binding fragment thereof

that binds specifically to Apo-3 polypeptide selected from the group consisting of the amino acid sequence comprising the amino acid residues 1 to 417 of SEQ ID NO:47[2] [sic], the extracellular domain of Apo-3 consisting of amino acid residues 25 to 198 of SEQ ID NO:6, the death domain of Apo-3 consisting of the amino acid residues 338 to 417 of SEQ ID NO:6 and a method of detecting Apo-3 using said antibody . . ." *Id.* Moreover, the Examiner acknowledges written description for the use of these antibodies "to block excessive apoptosis" or "block potential autoimmune/inflammatory effects of Apo-3 resulting from NF-κB activation." *See id.*

The Examiner has cited *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Univ. of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004) in support of the contention that the claims are not adequately supported. As the Applicant will explain, these cases fail to support the positions currently asserted by the Examiner. *Lilly*, for example involved claims encompassing certain human cDNA, however, no sequence information indicating which nucleotides constitute human insulin cDNA was provided in the claims or specification (only the sequence of rat insulin cDNA was provided).[3] The court noted that "cDNA is not defined or described by the mere name 'cDNA,' even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." *Lilly*, 43 USPQ2d at 1406. According to the Federal Circuit, the written description problem in *Univ. of Rochester* involved a similar problem – the specification did "not disclose any compounds that [could] be used in its claimed methods" and "[n]o compounds that will perform the claimed method [were] disclosed, nor [was] any evidence . . . shown that such a compound was known." *See Univ. of Rochester*, 69 USPQ2d at 1895. The Federal Circuit ultimately found that the specification of the patent in suit contained "no disclosure of any method for making even a single 'non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product'" as required in the claims. *See id.* at 1897.

In contrast to those considered in *Lilly* and *Univ. of Rochester*, the present claims involve the use of an antibody to human Apo-3. It is undisputed that the present specification

[2] They Applicant assumes that since SEQ ID NO:47 does not appear in the present application, the Examiner intended to refer to SEQ ID NO:6 instead of SEQ ID NO:47.
[3] The Applicant notes that the current claims are not specifically directed to cDNA or use thereof.

sets forth the specific amino acid sequence (SEQ ID NO:6) for human Apo-3, including the location and boundaries of several domains in this polypeptide. Moreover, cDNA encoding Apo-3 polypeptide (i.e., SEQ ID NO:6) has been deposited with the ATCC and is referenced in the specification as filed. *See, e.g.*, page 69, last paragraph; and page 77. The amino acid sequence of SEQ ID NO:6 forms a limitation of each of the pending claims. As indicated in *Noelle v. Lederman*, 69 USPQ2d 1508 (Fed. Cir. 2004), "as long as an applicant has disclosed a '*fully characterized* antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." *Id.* at 1514. Antibodies to Apo-3 polypeptides, therefore, are also adequately described in the present specification. Further, beyond structural characterization of the antigen, the specification also describes functional activities of the Apo-3 polypeptide (*see, e.g.*, Examples 6, 7 and 8) and the claims include corresponding functional limitations. As acknowledged by the Examiner, the specification clearly states that these Apo-3 antibodies "may be used to block excessive apoptosis" or "block potential autoimmune/inflammatory effects of Apo-3 resulting from NF-KB activation." *See, e.g.*, specification at pages 62-63.

Based on the arguments presented above, Applicant believes that the claims comply with the written description argument and requests that the Examiner remove the rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 52-53 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The examiner has indicated that "it is not clear to one of ordinary skill in the art how a labeled Apo-3 antibody could block or inhibit Apo-3 receptor induced apoptosis in mammalian cells of how a labeled antibody blocks or inhibits Apo-3 receptor activation of NFκB in mammalian cells." Office action, page 8, ¶ 10.

It appears that the Examiner is indicating that the existence of this limitation renders the claim indefinite because one of skill in the art could not determine what antibodies fall within the scope of the claims. It appears, therefore, that the Examiner is interpreting an antibody used to block or inhibit Apo-3 receptor induced apoptosis Apo-3 receptor activation of NFκB as *mutually exclusive* of anti-Apo-3 antibodies useful to detect Apo-3 in mammalian cells. The specification and claims do not require this interpretation and one of skill in the art would not interpret these categories as mutually exclusive.

The overlap in the antibody categories renders them definite since one could readily determine what antibodies have the requisite blocking or inhibiting activities and therefore fall within the scope of the claims. As discussed above, it is well known in the art that an antibody can be labeled without affecting its reactivity or binding specificity in, for example, a sandwich assay, a competitive binding assay or an immunoprecipitation assay. *See, e.g.*, specification at page 62. This antibody may be labeled and used to bind a receptor, for example, an Apo-3 polypeptide receptor. If the labeling process affects the ability of the antibody to block the selected activity, this too can be determined utilizing methods set forth in the specification and the resulting labeled antibody would be excluded from the scope of the claims as not having the requisite activity. Accordingly, the Applicant respectfully submits that this limitation is not indefinite.

Rejection Under 35 U.S.C. § 102(e)

Claims 46, 50-51, 54-55, 61 and 64-66 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by U.S. Patent No. 6,153,402 ("Yu *et al.*"). The Examiner has credited Yu *et al.* with the teaching of SEQ ID NO:4 identified therein. Based on this sequence, which the Examiner states is "100% identical to the claimed SEQ ID NO:6," the Examiner opines that Yu *et al.* "teaches a method of blocking apoptosis or inhibits [sic] Apo-3 receptor induced apoptosis comprising exposing mammalian cells expressing Apo-3 receptor to anti-Apo-3 antibody such as monoclonal antibody that binds to an Apo-3 receptor polypeptide comprising SEQ ID NO:4." Office action, page 4 ¶ 13. Moreover, the Examiner has noted the earliest filing date listed for Yu *et al.* as March 12, 1996. It appears, therefore, that the Examiner has accorded March 12, 1996 as the priority date for SEQ ID NO:4 of Yu *et al.* The Applicant respectfully traverses.

Yu *et al.* claims priority through three different provisional applications — U.S. Provisional Application No. 60/037,341, filed February 6, 1997; U.S. Provisional Application No. 60/028,711, filed October 17, 1996; and U.S. Provisional Application No. 60/013,285, filed March 12, 1996 ("the '285 application"). Only the earliest of these provisional applications, the '285 application, pre-dates the priority date currently accorded the pending claims. Therefore, the only relevant disclosure for determining whether Yu *et al.* anticipates under 35 U.S.C. § 102(e) is that of the '285 application. *See, e.g., In re Wertheim and Mishkin*, 209 USPQ 554 (CCPA 1981).

Yu *et al.* discloses two different polypeptides, referred to as DR3-V1 and DR3 respectively, encoded by cDNA nucleic acid sequences which were cloned from a cDNA library. The '285 application, however, disclosed *only* the sequence of DR3-V1[4]; the second sequence, DR3, was disclosed *for the first time* in the second priority application of Yu *et al.* filed October 17, 1996 and cannot, therefore, be prior art to the instant application. The fact that only DR3-V1 was disclosed in the earliest provisional application is significant because the DR3-V1 polypeptide, as disclosed in the '285 application, does not correspond to the Apo-3 polypeptide in overall sequence or the particular regions identified in the present claims. This is clearly evident by the alignment of the signal peptides of the DR3-V1 sequence disclosed in the '285 application and Apo-3 polypeptides below (bolded amino acid residues indicate identical residues).[5]

```
DR3-V1:    1    Met Glu Glu Thr Gln Gln Gly Glu Ala Pro 10
Apo-3:     1    Met Glu Gln Arg Pro Arg Gly Cys Ala Ala 10

DR3-V1:    11   Arg Gly Gln Leu Arg Gly Glu Ser Ala Ala 20
Apo-3:     11   Val Ala Ala Ala Leu Leu Leu Val Leu Leu 20

DR3-V1:    21   Pro Val Pro Gln Ala Leu Leu Leu Val Leu 30
Apo-3:     21   Gly Ala Arg Ala 24
```

As is clearly evident, the signal peptides of DR3-V1 and Apo-3 are very different when aligned from the first amino acid residue of each polypeptide. The Applicant notes that there is no indication in the '285 application that the deduced DR3-V1 polypeptide should be compared with other proteins, if at all, in any other way than from the first amino acid residue.

An alignment of the designated extracellular domains of the DR3-V1 and Apo-3 polypeptides is as follows:[6]

```
DR3-V1:    30   Leu Leu Gly Ala Arg Ala Gln Gly Gly Thr 39
Apo-3:     25   Gly Gly Thr Arg Ser Pro Arg Cys Asp Cys 34

DR3-V1:    40   Arg Ser Pro Arg Cys Asp Cys Ala Gly Asp 49
Apo-3:     35   Ala Gly Asp Phe His Lys Lys Ile Gly Leu 44

DR3-V1:    50   Phe His Lys Lys Ile Gly Leu Phe Cys Cys 59
Apo-3:     45   Phe Cys Cys Arg Gly Cys Pro Ala Gly His 54
```

[4] The '285 application refers to DR3-V1 as "DDCR." *See* Yu *et al.* Col. 3, ln. 22.
[5] The specification and claims of the '285 application are included herewith for the Examiner's reference.
[6] This region is referred to as the "ligand binding domain" in the '285 application.

```
DR3-V1:    60   Arg Gly Cys Pro Ala Gly His Tyr Leu Lys 69
Apo-3:     55   Tyr Leu Lys Ala Pro Cys Thr Glu Pro Cys 64

DR3-V1:    70   Ala Pro Cys Thr Glu Pro Cys Gly Asn Ser 79
Apo-3:     65   Gly Asn Ser Thr Cys Leu Val Cys Pro Gln 74

DR3-V1:    80   Thr Cys Leu Val Cys Pro Gln Asp Thr Phe 89
Apo-3:     75   Asp Thr Phe Leu Ala Trp Glu Asn His His 84

DR3-V1:    90   Leu Ala Trp Glu Asn His His Asn Ser Glu 99
Apo-3:     85   Asn Ser Glu Cys Ala Arg Cys Gln Ala Cys 94

DR3-V1:   100   Cys Ala Arg Cys Gln Ala Cys Asp Glu Gln 109
Apo-3:     95   Asp Glu Gln Ala Ser Gln Val Ala Leu Glu 104

DR3-V1:   110   Ala Ser Gln Val Ala Leu Glu Asn Cys Ser 119
Apo-3:    105   Asn Cys Ser Ala Val Ala Asp Thr Arg Cys 114

DR3-V1:   120   Ala Val Ala Asp Thr Arg Cys Gly Cys Lys 129
Apo-3:    115   Gly Cys Lys Pro Gly Trp Phe Val Glu Cys 124

DR3-V1:   130   Pro Gly Trp Phe Val Glu Cys Gln Val Ser 139
Apo-3:    125   Gln Val Ser Gln Cys Val Ser Ser Ser Pro 134

DR3-V1:   140   Gln Cys Val Ser Ser Ser Pro Phe Tyr Cys 149
Apo-3:    135   Phe Tyr Cys Gln Pro Cys Leu Asp Cys Gly 144

DR3-V1:   150   Gln Pro Cys Leu Asp Cys Gly Ala Leu His 159
Apo-3:    145   Ala Leu His Arg His Thr Arg Leu Leu Cys 154

DR3-V1:   160   Arg His Thr Arg Leu Leu Cys Ser Arg Arg 169
Apo-3:    155   Ser Arg Arg Asp Thr Asp Cys Gly Thr Cys 164

DR3-V1:   170   Asp Thr Asp Cys Gly Thr Cys Leu Pro Gly 179
Apo-3:    165   Leu Pro Gly Phe Tyr Glu His Gly Asp Gly 174

DR3-V1:   180   Phe Tyr Glu His Gly Asp Gly Cys Val Ser 189
Apo-3:    175   Cys Val Ser Cys Pro Thr Ser Thr Leu Gly 184

DR3-V1:   190   Cys Pro Thr Ser Thr Leu Gly Ser Cys Pro 199
Apo-3:    185   Ser Cys Pro Glu Arg Cys Ala Ala Val Cys 194

DR3-V1:   200   Glu Arg Cys Ala Ala Val Cys Gly Trp Arg 209
Apo-3:    195   Gly Trp Arg Gln 198

DR3-V1:   210   Gln Met Phe Trp Val 215
```

As is also evident from the above alignment, the extracellular domains of DR3-V1 and Apo-3 are very different.

Finally, an alignment of the designated death domains of the DR3-V1 and Apo-3 polypeptides is as follows:

```
DR3-V1:    350  Met Asp Ala Val Pro Ala Arg Arg Trp Lys 359
Apo-3:     338  Val Met Asp Ala Val Pro Ala Arg Arg Trp 347

DR3-V1:    360  Glu Phe Val Arg Thr Leu Gly Leu Arg Glu 369
Apo-3:     348  Lys Glu Phe Val Arg Thr Leu Gly Leu Arg 357

DR3-V1:    370  Ala Glu Ile Glu Ala Val Glu Val Glu Ile 379
Apo-3:     358  Glu Ala Glu Ile Glu Ala Val Glu Val Glu 367

DR3-V1:    380  Gly Arg Phe Arg Asp Gln Gln Tyr Glu Met 389
Apo-3:     368  Ile Gly Arg Phe Arg Asp Gln Gln Tyr Glu 377

DR3-V1:    390  Leu Lys Arg Trp Arg Gln Gln Gln Pro Ala 399
Apo-3:     378  Met Leu Lys Arg Trp Arg Gln Gln Gln Pro 387

DR3-V1:    400  Gly Leu Gly Ala Val Tyr Ala Ala Leu Glu 409
Apo-3:     388  Ala Gly Leu Gly Ala Val Tyr Ala Ala Leu 397

DR3-V1:    410  Arg Met Gly Leu Asp Gly Cys Val Glu Asp 419
Apo-3:     398  Glu Arg Met Gly Leu Asp Gly Cys Val Glu 407

DR3-V1:    420  Leu
Apo-3:     408  Asp Leu Arg Ser Arg Leu Gln Arg Gly Pro 417
```

As is similarly evident from the above alignment, the death domains of DR3-V1 and Apo-3 are markedly different.

To the extent the '285 application contemplates fragments of the deduced DR3-V1 polypeptide, no fragments having any likeness to the Apo-3 polypeptide of the present claims are identified in the '285 application. Moreover, the '285 application fails to discuss any specific sequence frame shifts, inversions, repeats, additions or deletions that would result in a polypeptide having any likeness to the Apo-3 polypeptide of the present claims. It is possible that the Examiner may have relied on such alterations in the deduced DR3-V1 polypeptide sequence but has not identified where in the '285 application one may locate the basis for the suggested alterations nor indicated that they are inherent aspects of the deduced DR3-V1 polypeptide.

Accordingly, the above alignments provide evidence supporting the Applicant's position that the deduced DR3-V1 polypeptide does not correspond to, and therefore does not anticipate under § 102(e), the Apo-3 polypeptide of the present claims.

In addition, to the extent the '285 application provides any direction to a signal peptide (amino acid residues 1-30 – *see* page 7, lines 34-35), extracellular domain (amino acid residues 30-215 - *see* page 7, line 35), transmembrane domain (amino acid residues 215-

240 – *see* page 8, line 1), intracellular domain (amino acid residues 240-428 – *see* page 8, lines 1-2) or death domain (amino acid residues 350-420 – *see* page 8, lines 2-3), it points to completely different domains having different boundaries within its longer 428 amino acid DR3-V1 (DDCR) polypeptide versus the polypeptide of the present claims.[7] *See* '285 application at page 7, line 34-page 8, line 3; page 11, lines 10-19; Figure 1; SEQ ID NO:1 as is illustrated in the sequence alignments above.

In this regard, the Applicant notes that the domains (e.g., the signal sequence, extracellular domain, transmembrane domain, intracellular domain and death domain) of DR3-V1 set forth in Yu *et al.* are not those set forth for DR3-V1 in the '285 application. Compare the '285 application at page 7, line 34-page 8, line 3; page 11, lines 10-19 with Yu *et al.* at col. 4, lines 25-31. The table below summarizes the changes to these domains between the '285 application and Yu *et al.*:

DR3-V1 Domain	**'285 application (SEQ ID NO:2) Amino Acid Position Nos.**	**Yu *et al.* (SEQ ID NO:2) Amino Acid Position Nos.**
Signal peptide	1-30	1-35
Extracellular domain	30-215	36-212
Transmembrane domain	215-240	213-235
Intracellular domain	240-428	236-428
Death domain	350-420	353-419

Each of these domains were changed, without explanation, in applications filed after the '285 application. *See id.*; *see also* Application No. 60/028,711 at page 6, lines 15-19 (The specification and claims of the '711 application are included herewith for the Examiner's reference). One likely explanation for these changes is that sometime between the filing of the '285 and the application giving rise to Yu *et al.*, the inventors of the '285 application

[7] *See In re Arkley*, 172 USPQ 524 (CCPA 1972) ("[F]or the instant rejection under 35 USC 102(e) to have been proper, the . . . reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."); *see also Sunitiger, Inc. v. Blublocker*, 51 USPQ2d 1811, 1818 (Fed. Cir. 1999) ("The case law makes clear that disclosure of a generic expression encompassing a large number of possible variants is not a description of all of them." *Id.* (citing In re *Ruschig*, 154 USPQ 118, 121 (CCPA 1967) (finding that a disclosure of a class of compounds did not provide descriptive support for a single compound within the class *not specifically identified* in the specification); and *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1904-05 (Fed. Cir. 1996) (finding no descriptive support even when the proposed genus was actually disclosed in the specification due to the *lack of direction* that would lead one of skill to the proposed subgenus)).

realized that they inaccurately estimated the positions of each of the DR3-V1 polypeptide domains in the '285 application. In fact, Yu *et al.* acknowledges that the position of the signal sequence cleavage site, for example, may have been predicted using a method having only about 75-80% accuracy. *See* Yu *et al.* at col. 6, lines 50-59 (a disclosure that was provided in Yu *et al.*, but not in the '285 application). Clearly, a question of descriptive support for, and enablement of, any DR3-V1 polypeptide that may exist in nature arises in light of the comparison of the '285 application and Yu *et al.* disclosures. Moreover, confusion by the Yu *et al.* and '285 application inventors about aspects of the deduced DR3-V1 polypeptide cannot be reasonably interpreted as an inherent disclosure of the Apo-3 polypeptide of the present claims, with each of its limitations. *See Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) ("Inherency, however, may not be established by probabilities or possibilities.").

Accordingly, the Yu, *et al.* reference is not an effective anticipatory reference under § 102(e) as its priority applications do not describe, in a manner sufficient under § 112, each of the limitations of the pending claims.

Rejections Under 35 U.S.C. § 103(a)

Claims 47-49 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Yu *et al.* in view of U.S. Patent No. 6,180,370.

The basis for citation of Yu *et al.* as the primary reference in the Examiner's obviousness analysis lies solely in its purported status as a prior art reference under 35 U.S.C. § 102(e). As indicated above, Yu *et al.* is not an effective anticipatory reference under 102(e) as its priority applications do not describe each of the limitations of the pending claims. U.S. Patent No. 6,180,370 is cited for generic teachings of "chimeric" and "humanized" antibodies and fails to fill the gaps left by Yu *et al.* Accordingly, the present obviousness rejection of claims 46-49 cannot be maintained. Withdrawal is respectfully requested.

Claims 52-53 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Yu *et al.* in view of Harlow *et al.*

The basis for citation of Yu *et al.* as the primary reference in the Examiner's obviousness analysis lies solely in its purported status as a prior art reference under 35 U.S.C. § 102(e). As indicated above, Yu *et al.* is not an effective anticipatory reference under 102(e)

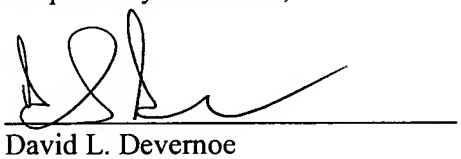
as its priority applications do not describe each of the limitations of the pending claims. Harlow *et al.* is cited for generic teachings of labeling antibodies and monoclonal antibodies and fails to fill the gaps left by Yu *et al.* Accordingly, the present obviousness rejection of claims 52-53 cannot be maintained. Withdrawal is respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully submits that all pending claims as currently presented are in condition for allowance. Favorable reconsideration is respectfully requested.

In the unlikely event that the Patent Office determines that extensions and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or fees due to our Deposit Account No. **18-1260**, referencing Docket No. **22338-1205**. Any refund should be credited to the same account. The Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,



David L. Devernoe
Registration No. 50,128
Attorney for Applicant

Date: 1/17/06

SIDLEY AUSTIN BROWN LLP
1501 K Street, N.W.
Washington, DC 20005
202-736-8000